Medical Progress

Intracavitary Chemotherapy for Malignant Disease Confined to Body Cavities

MAURIE MARKMAN, MD, San Diego

The direct administration of cytotoxic chemotherapeutic agents into the peritoneal or pleural cavities to treat malignant disease principally involving these regions is based on modeling studies suggesting a major pharmacokinetic advantage for the exposed cavity compared with the plasma. The safety and clinical efficacy of several agents administered directly into body cavities either singly or in combination have now been shown. Additional studies are needed to define optimal drugs, dosages and treatment schedules for the various tumors confined to body cavities. Whether this form of therapy will prove to be superior to standard systemic drug administration will require controlled clinical trials comparing the two treatment methods.

(Markman M: Intracavitary chemotherapy for malignant disease confined to body cavities [Medical Progress]. West J Med 1985 Mar; 142:364-368)

While the systemic administration of chemotherapeutic agents will result in satisfactory delivery of drug to well-vascularized regions of the body, there is legitimate concern that this approach to the delivery of cytotoxic therapy might not be optimal for tumors confined to body cavities. To improve the efficacy of therapy for malignant disease in the pleural and peritoneal cavities, investigators have attempted to administer drugs directly into the region being treated. While *intracavitary chemotherapy* has frequently been used as a method to produce sclerosis and prevent reaccumulation of malignant effusions, recent modeling studies have suggested that this might be an excellent approach to the delivery of drugs administered for their cytotoxic properties.[1] Following a brief discussion of sclerosing therapy, I will highlight some of the major principles of intracavitary chemotherapy and will conclude with examples of the potential utility of this modality in patients with malignant disease principally confined to body cavities.

Intracavitary Chemotherapy Administered for Its Sclerosing Properties

The administration of chemotherapeutic agents directly into body cavities is not a new concept. In the early days of the medical use of alkylating agents, mechlorethamine hydrochloride, a nitrogen mustard, was instilled into the peritoneum of patients with malignant ascites in an effort to kill tumor and prevent fluid accumulation.[2] Initial reports suggested significant reductions in the rate of ascites formation

following treatment with mechlorethamine, hemisulfur mustard and thiotepa administered by the intracavitary route.[2-4] While the investigators involved in these early studies suggested that the alkylating agents were directly cytotoxic to cancer cells, there was little evidence of shrinkage of any mass lesion, and it is much more likely that the drugs were acting as *sclerosing agents*. Pain was often severe in patients receiving intracavitary chemotherapy and, as a result, this form of therapy became reserved for patients with recurrent pleural effusions and intractable ascites.

Several chemotherapeutic agents have shown major utility in controlling malignant effusions. While mechlorethamine is used less often today because of the pain it produces, the agent is effective in controlling the reaccumulation of pleural effusions in as many as 40% of patients treated.[5,6] The use of bleomycin sulfate has produced complete and partial response rates in controlling pleural effusions of 60%.[7,8] Patients with effusions due to breast carcinoma appear to respond more favorably than patients with lung cancer. The agent is less effective in preventing the reaccumulation of ascitic fluid. Local pain and fever are the most frequently reported side effects. Several different dose schedules of bleomycin have been effective in inducing sclerosis, with the optimal dose being 60 units in 100 ml of saline.[8]

Doxorubicin hydrochloride has also been a useful agent in inducing sclerosis in the pleural and peritoneal cavities and in preventing fluid reaccumulation.[5] In one study, 12 of 15 patients (80%) with effusions responded to the intracavitary

administration of doxorubicin, with three patients having complete clearance of fluid for a minimum of two months. The dose of doxorubicin administered in this study was 30 mg in 25 ml of normal saline.

While the optimal management of malignant effusions and ascites has not been clearly defined, the administration of several chemotherapeutic agents or tetracycline[9] directly into the body cavity to be treated has been at least partially effective palliation in about 50% to 60% of patients treated.[10] The major toxic effect is usually local pain. This can frequently be decreased by the simultaneous administration of lidocaine along with the sclerosing therapy. Drainage of as much fluid as possible before instilling the drug is an important principle in assuring the best possible result of therapy and chest tube drainage both before and after the administration of chemotherapy is frequently done.

Effective treatment regimens for sclerosis of body cavities use *high* concentrations of drug in *small* treatment volumes. This contrasts sharply with the basic principles of intracavitary therapy for the delivery of chemotherapeutic agents administered for their cytotoxic properties, as will be discussed further.

Principles of Intracavitary Chemotherapy Administration

The first and one of the most important steps in the ability of a chemotherapeutic agent to kill a malignant cell is delivery of the drug to the tumor in the highest concentration possible. As previously mentioned, drugs administered systemically have access to well-vascularized organs such as the bone marrow or gut. Because of longer diffusional distances, however, it is likely that chemotherapeutic agents given intravenously will have much lower penetration into extravascular cavities, such as the pleural space, peritoneal cavity and central nervous system. From theoretic modeling a major possible pharmacokinetic advantage has been suggested for drugs administered directly into body cavities.[1] While the details of such mathematical modeling studies are beyond the scope of this review, the basic principles they define are important to understand the rationale behind direct intracavitary administration of chemotherapeutic agents (Figure 1).

When a drug is infused into an extravascular cavity, the steady-state concentration in the cavity and plasma is a function of the *rate of clearance* from the cavity and plasma. For drugs that demonstrate *low* clearance from the cavity and *high systemic* clearance, there will be a pharmacokinetic advantage for the cavity into which the drug has been instilled compared with the systemic circulation.[1] Important determinants of clearance include the molecular weight of the drug, its charge, lipid solubility and the volume of fluid in which the drug is administered.[11] A drug with a low clearance from a body cavity would be one that has a high molecular weight, is ionized and water soluble and is administered in a large treatment volume.

A second important issue relates to the metabolism of the administered drug. Molecules the size of chemotherapeutic agents are principally taken up in the portal circulation when

instilled in the peritoneal cavity.[12-14] Thus, a drug administered intraperitoneally that is hepatically metabolized might show a major pharmacokinetic advantage when administered by this route if it can be converted into a nontoxic metabolite before entering the systemic circulation.

A third principle for the successful application of intracavitary chemotherapy is the importance of treatment volume.[15-17] When drugs are delivered for their sclerosing properties, high concentrations are administered in small volumes. To prevent sclerosis and insure adequate exposure of drug to all tumor in the cavity, it is important to deliver the treatment in *large* volumes. In animals[18] and in several clinical trials,[19,20] the importance of treatment volume in overcoming the problems of drug distribution during intraperitoneal chemotherapy has been convincingly shown. This is a particularly important issue in many patients with intra-abdominal malignant lesions, as extensive adhesion formation induced by a prior surgical procedure or the tumor itself can possibly prevent access of drug to the entire abdominal cavity.

An additional question concerning the applicability of intracavitary chemotherapy is that of drug penetration. Little is known about the ability of most chemotherapeutic agents to penetrate into solid tumors.[21,22] Because of its intrinsic fluorescence, Ozols and co-workers were able to examine the penetrability of doxorubicin in a transplantable murine ovarian teratoma.[23] Whereas doxorubicin was found in only the outermost five to six cell layers of tumor when administered by the intraperitoneal route, this form of treatment was successful in curing 70% of the mice treated. When mice with this tumor were similarly treated with a regimen of intravenously administered doxorubicin, there were no long-term survivors.[24]

Theoretically, the intracavitary form of therapy will be most effective against free-floating tumor cells or thin tumor nodules. Free surface diffusion is unlikely to kill a large fraction of tumor in cases of advanced disease where large tumor masses are present. However, if drugs are used at or near their

Chemotherapeutic Agent
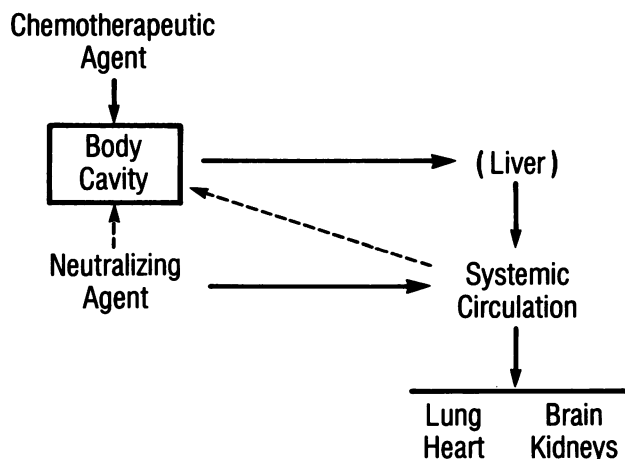
Figure 1.—Diagrammatic presentation of the basic principles of intracavitary chemotherapy. A drug administered via the intracavitary route will be absorbed into the systemic circulation at a rate determined by its physical and chemical characteristics. Drugs administered intraperitoneally can be metabolized in the liver into a nontoxic form before entering the systemic circulation. Finally, this treatment approach allows for the use of systemically delivered neutralizing agents to further enhance the pharmacokinetic advantage (see text).

maximum tolerated doses, then the combination of drug delivery by capillary flow (from drug absorbed into the systemic circulation) and free surface diffusion may still be more effective than intravenous dosing alone.

Finally, the large concentration differences achieved between the body cavity and plasma present the opportunity to make use of neutralizing agents delivered into the systemic circulation to reduce toxicity, while allowing high levels of drug to be present in the cavity treated. Two examples of this technique that have been clinically useful are the use of systemically delivered folinic acid[25,26] and sodium thiosulfate[20,27] administered to neutralize the toxicities of methotrexate and cisplatin, respectively. Results of clinical trials using these two neutralizing agents will be discussed in the following section.

Mention should also be made of the practical difficulties associated with intracavitary chemotherapy. Drug escaping from the body cavity can cause systemic side effects. In fact, if no local toxic reaction is encountered, dose-limiting toxicity will be similar to that seen when the agent is administered systemically. However, certain drugs might be quite irritating to the serosal surfaces and lead to pain and fever (chemical peritonitis or pleuritis), which must be distinguished from infectious causes. In addition, inflammation induced by the chemotherapeutic agent might result in adhesion formation, which can interfere with drug distribution and lead to bowel obstruction or loss of pulmonary function.

The delivery of drugs into body cavities requires a safe delivery system. Patients with a large volume of ascites or pleural effusions can be treated by the percutaneous placement of catheters specifically used to deliver the treatment. However, patients without such fluid or those responding to therapy with a decrease in malignant effusions require the surgical placement of semipermanent indwelling catheters to administer the treatment volume. There is significant experience in the safe use of such systems in patients requiring peritoneal dialysis, and similar devices have been adapted for use in patients being treated with intracavitary chemotherapy. Unfortunately, with indwelling catheters there is the risk of contamination of the system with the administration of therapy or with manipulation to drain fluid or inject heparin.

Single-Agent Intracavitary Chemotherapy

5-Fluorouracil has been evaluated for its safety and utility when administered by the intraperitoneal route.[14,28,29] In a clinical trial conducted at the National Cancer Institute (NCI), ten patients with refractory malignant tumors were treated with concentrations of 5-fluorouracil from 5 μmol to 8 mmol per liter (1.3 to 2,080 mg) in two liters of fluid. Dose-limiting toxic effects included pancytopenia and mucositis at concentrations of 4.5 mmol per liter. Abdominal pain was also significant and bacterial peritonitis developed in several patients. Objective antitumor responses were observed in several patients with ovarian carcinoma for whom standard chemotherapy given intravenously had previously failed.[28,29] A major pharmacokinetic advantage for peritoneal cavity drug exposure was shown (Table 1). In a second study, the NCI investigators found that total drug delivery of 5-fluorouracil to the liver via the portal circulation following intraperitoneal therapy was comparable with that achieved following direct intra-arterial drug administration.[14] However, additional

TABLE 1.—*Pharmacokinetic Advantage of Intraperitoneal Drug Administration*

Drug	*Mean Peak Peritoneal/Plasma Concentration Ratio*	*Sources*
Cytarabine	664	King and Howell[30]
5-Fluorouracil	298	Speyer et al[14,28]
Methotrexate	92	Howell et al[26]
Doxorubicin hydrochloride	474	Ozols et al[31]
Melphalan	93	Pfeifle et al[32]
Cisplatin	20	Howell et al[20]
Mitomycin	71	Adams et al[33]

trials will need to be conducted to define the safety and efficacy of the intraperitoneal approach to the treatment of metastatic disease in the liver. This is particularly important as it is known that 95% of the blood supply to a large metastatic lesion in the liver comes from the hepatic artery, with only 5% being delivered via the portal circulation.[34]

As previously mentioned, the intracavitary administration of methotrexate allowed one to examine the utility of a systemically administered neutralizing agent. Investigators at the NCI delivered increasing dosages of methotrexate intracavitarily, with folinic acid rescue administered as a continuous infusion from 40 to 56 hours after the initiation of the methotrexate infusion.[25] While no definite clinical activity was shown in this trial, toxic reaction was mild and a significant pharmacokinetic advantage for peritoneal cavity drug exposure was found (Table 1). In a trial conducted at the UCSD Cancer Center, folinic acid was administered systemically simultaneously with the intracavitary delivery of methotrexate.[26] Toxic effects included mild abdominal pain and myelosuppression. Responses were observed in several patients with advanced refractory malignant tumors. These two clinical trials show contrasting approaches to the use of neutralizing agents. In the NCI trial the folinic acid was administered as a *rescue* agent following intracavitary drug delivery. In the UCSD trial the two drugs were given simultaneously. This allows for longer exposure of the body cavity to the cytotoxic agent, a major possible therapeutic advantage for a cell-cycle phase-specific agent such as methotrexate. Unfortunately, this latter technique runs the risk of neutralizing the methotrexate by the diffusion of folinic acid from the systemic circulation into the treated cavity (Figure 1).

The intraperitoneal administration of doxorubicin has been examined at the NCI.[31] Ten patients with refractory ovarian carcinoma were treated with doxorubicin at from 10 to 50 mg (9 to 54 μmol) in a two-liter treatment volume. None of the patients had previously received doxorubicin. There were five clinical responses including objective evidence of tumor regression in three patients and decrease in ascites in two additional patients. A dose-limiting toxic effect was abdominal pain at greater than 40 mg (36 μmol) in the two-liter volume. However, in spite of local toxic reaction limiting the dose of doxorubicin that could be administered intraperitoneally, a significant pharmacokinetic advantage for this route of drug delivery was shown (Table 1).

The safety and efficacy of the intracavitary delivery of cisplatin, one of the most active chemotherapeutic agents in ovarian carcinoma,[35] have been examined by several investigators.[20,36,37] As previously discussed, the simultaneous intravenous delivery of sodium thiosulfate administered to pre-

vent renal insufficiency caused by cisplatin has allowed the dose of this agent to be significantly escalated. Thiosulfate, an agent used clinically in high doses in humans for cyanide poisoning, had previously been found in mice to significantly protect against the nephrotoxicity of cisplatin.[38] This agent presumably combines with and inactivates the reactive site on cisplatin, neutralizing both its toxic and antitumor effects.

In a clinical trial conducted at the UCSD Cancer Center, cisplatin was able to be administered at a dose of 270 mg per m² (compared with the maximum intravenous dose of 120 mg per m²) with minimal nephrotoxicity.[20] The cisplatin was administered in a volume of two liters with a four-hour dwell, after which any remaining fluid was removed. Only 7% of the instilled cisplatin could be recovered at the end of the four-hour dwell period. Myelosuppression was mild in this trial but cisplatin-induced emesis was substantial. The peak peritoneal concentration of free reactive cisplatin averaged 21-fold higher than plasma levels and the area under the concentration elimination curve averaged 12-fold more than under the plasma curve. What was perhaps most interesting, however, was that the area under the concentration curve for the plasma (at a dose of 270 mg per m²) increased twofold compared with that for cisplatin administered intravenously at a dose of 100 mg per m². It is our hypothesis that whereas sodium thiosulfate does neutralize cisplatin, this reaction is slow at the concentration of thiosulfate in the plasma, but proceeds rapidly and completely in the kidney where the thiosulfate is concentrated.[39] Objective responses were shown in a number of patients with advanced intra-abdominal malignant lesions treated on this trial.

As unexpected activity of the intracavitary administration of cisplatin was found in several patients with malignant mesothelioma—a tumor that remains localized to the pleural or peritoneal cavities for much of its natural history[40]—a trial of this form of therapy has been conducted at our center to better define its efficacy.[41] A response rate of about 50% has been observed that is equal to that reported with intravenous administration of doxorubicin, the most active agent in this disease.[42] Cisplatin administered intravenously has a reported response rate of only 10% in cases of malignant mesothelioma.[42]

Melphalan has also been examined for intraperitoneal drug administration.[32,43] Whereas a pharmacokinetic advantage has been shown for the drug administered by this route (Table 1) with acceptable local toxic effect, there has been little clinical activity shown in patients with refractory tumors. However, with the demonstrated ability of this agent to achieve both high local and systemic concentrations when administered intraperitoneally, a strong argument can be made that this is the most rational method by which to deliver this agent to patients who have ovarian carcinoma.[32]

Investigators have evaluated the intraperitoneal delivery of mitomycin to patients who have advanced intra-abdominal tumors.[33,44] Whereas increased peritoneal cavity exposure to this drug has occurred compared with the plasma and clinical responses that have been noted, in several patients treated with this agent a chemical peritonitis developed.

Cytarabine was predicted on the basis of modeling studies to have a major pharmacokinetic advantage when administered intraperitoneally.[1] This agent is rapidly inactivated by deamination in the liver,[45] and, as previously mentioned, the

absorption of compounds delivered intraperitoneally is principally through the portal circulation.[13] In addition to confirming the modeling predictions (Table 1), in a recent clinical trial both the safety and efficacy of the intraperitoneal administration of cytarabine in cases of ovarian cancer have been shown.[30] Ten patients with refractory ovarian carcinoma were treated with 60 μmol cytarabine (30 mg in a two-liter treatment volume) every six hours by dialysis exchange for five days. Treatment was repeated every 28 days. Two patients had complete clinical remissions that have persisted for longer than one year. Systemic side effects, principally myelosuppression, were mild and there was no local toxic reaction noted. Unfortunately, several episodes of bacterial peritonitis developed during the 20 courses of cytarabine administered during this trial.

Combination Intracavitary Chemotherapy

The superiority of combination chemotherapy over the administration of single agents in treating malignant disease has a sound theoretic basis (decreased emergence of resistant cells)[46,47] and has been confirmed clinically. In cases of several different types of tumors, combination therapy has been successful in producing complete responses whereas the use of single agents has resulted in only partial remissions. A second possible advantage for the administration of a combination of drugs during intracavitary chemotherapy is the potential for antitumor synergy among the agents used. For example, pronounced synergy has been shown in vitro between cisplatin and cytarabine against Lovo cells (a transplantable colon cancer cell line).[48-50] With the highest dose of cytarabine tested, a remarkable 1,600-fold increased cell kill occurred with this treatment combination compared with the use of cisplatin alone.

In a recently completed clinical trial at the UCSD Cancer Center, 31 patients with advanced intra-abdominal malignant tumors were treated with a combination of cisplatin, cytarabine and doxorubicin.[51] The toxic effects were acceptable except for doxorubicin-induced local abdominal pain. Responses, including considerable decreases in ascites and conversion of positive peritoneal cytologies to negative, occurred in 7 of 15 patients with ovarian carcinoma for whom intravenous chemotherapy regimens, including cisplatin, had previously failed. In a second trial, the dose of cytarabine was increased to take further advantage of possible concentration-dependent synergy betwen cisplatin and cytarabine. Doxorubicin was dropped from the treatment regimen to reduce local toxic effects. About 40% of patients with refractory ovarian carcinoma had objective responses to this program with significantly less abdominal pain compared with the previously mentioned three-drug combination.[52]

Combination intracavitary chemotherapy has also been effective in treating malignant pleural disease. Patients treated with either cisplatin, cytarabine and doxorubicin or cisplatin and cytarabine have shown dramatic decreases in the rate of reaccumulation of pleural fluid.[53] For several reasons it is believed the responses in patients treated with these treatment combinations are not due solely to the induction of sclerosis. First, none of the patients treated had local pain, a common and often severe complication of sclerosing therapy. Second, chest tube drainage was not used as part of the treatment program, an important component of most sclerosing treat-

ment regimens. Finally, several responses were observed in patients ten days to two weeks after therapy was administered, with patients initially showing rapid reaccumulation of fluid. This would suggest that the drugs are not acting directly on the pleural surfaces but rather on the tumor cells themselves, and it is only when the tumor has been killed and removed that a decrease in fluid reaccumulation will occur.

Conclusion

The field of intracavitary chemotherapy is in its infancy. Much work remains to be done to define optimal drug combinations and schedules for the various tumors to be treated by this route of drug administration. In addition, improved methods of delivery must be developed to assure adequate drug distribution and reduce the risk of chemical irritation and bacterial infection. Finally, it will eventually be necessary to show in controlled clinical trials whether the pharmacokinetic advantage of intracavitary drug administration can be translated into improved response rates and survival.

REFERENCES

1. Dedrick RL, Myers CE, Bungay PM, et al: Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep 1978; 62:1-9

2. Weisberger AS, Levine B, Storaasli JP: Use of nitrogen mustard in treatment of serous effusions of neoplastic origin. JAMA 1955; 159:1704-1707

3. Green TH: Hemisulfur mustard in the palliation of patients with metastatic ovarian carcinoma. Obstet Gynecol 1959; 13:383-393

4. Kottmeier HL: Treatment of ovarian carcinomas with thiotepa. Clin Obstet Gynecol 1968; 11:428-438

5. Kefford RF, Wood RL, Fox RM, et al: Intracavitary adriamycin, nitrogen mustard and tetracycline in the control of malignant effusions. Med J Aust 1980; 2:447-448

6. Anderson CB, Philpott GW, Ferguson TB: The treatment of malignant pleural effusions. Cancer 1974; 33:916-922

7. Paladine W, Cunningham TJ, Sponzo R, et al: Intracavitary bleomycin in the management of malignant effusions. Cancer 1976; 38:1903-1908

8. Ostrowski MJ, Halsall GM: Intracavitary bleomycin in the management of malignant effusions: A multicenter study. Cancer Treat Rep 1982; 66:1903-1907

9. Bayly TC, Kisner DL, Sybert A, et al: Tetracycline and quinacrine in the control of malignant pleural effusions. Cancer 1978; 41:1188-1192

10. Leff A, Hopewell PC, Costello J: Pleural effusion from malignancy. Ann Intern Med 1978; 88:532-537

11. Torres IJ, Litterst CL, Guarino AM: Transport of model compounds across the peritoneal membrane in the rat. Pharmacology 1978; 17:330-340

12. Kraft AR, Tompkins RK, Jesseph JE: Peritoneal electrolyte absorption: Analysis of portal, systemic venous and lymphatic transport. Surgery 1968; 64:148-153

13. Lukas G, Brindle SD, Greengard P: The route of absorption of intraperitoneally administered compounds. J Pharmacol Exp Ther 1971; 178:562-566

14. Speyer JL, Sugarbaker PH, Collins JM, et al: Portal levels and hepatic clearance of 5-fluorouracil after intraperitoneal administration in humans. Cancer Res 1981; 41:1916-1922

15. Tully TE, Goldberg ME, Loken MK: The use of ^{99m}Tc-sulfur colloid to assess the distribution of ^{32}P chromic phosphate. J Nucl Med 1974; 15:190-191

16. Taylor A Jr, Baily NA, Halpern SE, et al: Loculation as a contraindication to intracavitary ^{32}P chromic phosphate therapy. J Nucl Med 1975; 16:318-319

17. Vider M, Deland FM, Maruyama Y: Loculation as a contraindication to intracavitary ^{32}P chromic phosphate therapy. J Nucl Med 1976; 17:150-151

18. Rosenshein N, Blake D, McIntyre PA, et al: The effect of volume on the distribution of substances instilled into the peritoneal cavity. Gynecol Oncol 1978; 6:106-110

19. Dunnick NR, Jones RB, Doppman JL, et al: Intraperitoneal contrast infusion for assessment of intraperitoneal fluid dynamics. AJR 1979; 133:221-223

20. Howell SB, Pfeifle CE, Wung WE, et al: Intraperitoneal cisplatin with systemic thiosulfate protection. Ann Intern Med 1982; 97:845-851

21. West GW, Weichselbau R, Little JB: Limited penetration of methotrexate into human osteosarcoma spheroids as a proposed model for solid tumor resistance to adjuvant chemotherapy. Cancer Res 1980; 40:3665-3668

22. Durand RE: Flow cytometry studies of intracellular adriamycin in multicell spheroids in vitro. Cancer Res 1981; 41:3495-3498

23. Ozols RF, Locker GY, Doroshow JH, et al: Pharmacokinetics of adriamycin and tissue penetration in murine ovarian cancer. Cancer Res 1979; 39:3209-3214

24. Ozols RF, Grotzinger KR, Fisher RI, et al: Kinetic characterization and response to chemotherapy in a transplantable murine ovarian cancer. Cancer Res 1979; 39:3202-3208

25. Jones RB, Collins JM, Myers CE, et al: High-volume intraperitoneal chemotherapy with methotrexate in patients with cancer. Cancer Res 1981; 41:55-59

26. Howell SB, Chu BCF, Wung WE, et al: Long-duration intracavitary infusion of methotrexate with systemic leucovorin protection in patients with malignant effusions. J Clin Invest 1981; 67:1161-1170

27. Howell SB, Pfeifle, CE, Wung WE: Intraperitoneal cisplatin with systemic thiosulfate protection. Cancer Res 1983; 43:1426-1431

28. Speyer JL, Collins JM, Dedrick RL, et al: Phase I pharmacological studies of 5-fluorouracil administered intraperitoneally. Cancer Res 1980; 40:567-572

29. Speyer JL, Myers CE: The use of peritoneal dialysis for delivery of chemotherapy to intraperitoneal malignancies. Recent Results Cancer Res 1980; 74:264-269

30. King ME, Howell SB: Intraperitoneal cytarabine therapy in ovarian carcinoma. J Clin Oncol 1984; 2:662-669

31. Ozols RF, Young RC, Speyer JL, et al: Phase I and pharmacological studies of adriamycin administered intraperitoneally to patients with ovarian cancer. Cancer Res 1982; 42:4265-4269

32. Pfeifle CE, Howell SB, Olshen RA, et al: Intraperitoneal melphalan: A phase I study. Proc Am Soc Clin Pharm Ther 1983; 32:223

33. Adams SC, Patt YZ, Rosenblum MG: Pharmacokinetics of mitomycin C following intraperitoneal administration of mitomycin C and floxuridine for peritoneal carcinomatosis. Proc Am Assoc Cancer Res 1984; 25:361

34. Neiderhuber JE, Ensminger WE: Surgical considerations in the management of hepatic neoplasia. Semin Oncol 1983; 10:135-147

35. Katz ME, Schwartz PE, Kapp DS, et al: Epithelial carcinoma of the ovary: Current strategies. Ann Intern Med 1981; 95:98-111

36. Casper ES, Kelsen DP, Alcock NW, et al: IP cisplatin in patients with malignant ascites: Pharmacokinetic evaluation and comparison with the iv route. Cancer Treat Rep 1983; 67:235-238

37. Pretorius RG, Hacker NF, Berek JS, et al: Pharmacokinetics of IP cisplatin in refractory ovarian carcinoma. Cancer Treat Rep 1983; 67:1085-1092

38. Howell SB, Taetle R: Effect of sodium thiosulfate on cis-dichlorodiamineplatinum (II) toxicity and antitumor activity in L1210 leukemia. Cancer Treat Rep 1980; 64:611-616

39. Shea M, Koziol JA, Howell SB: Kinetics of sodium thiosulfate, a cisplatin neutralizer. Clin Pharmacol Ther 1984; 35:419-425

40. Antman KH, Blum RH, Greenberger JS, et al: Multimodality therapy for malignant mesothelioma based on a study of natural history. Am J Med 1980; 68:356-362

41. Pfeifle CE, Howell SB, Markman M: Intracavitary cisplatin for mesothelioma. Proc Am Soc Clin Oncol 1984; 3:258

42. Aisner J, Wiernik PH: Chemotherapy in the treatment of malignant mesothelioma. Semin Oncol 1981; 8:335-343

43. Holcenberg J, Anderson T, Ritch P, et al: Intraperitoneal chemotherapy with melphalan plus glutaminase. Cancer Res 1983; 43:1381-1388

44. Gyves J, Ensminger W, Niederhuber J, et al: Phase I study of intraperitoneal (IP) 5 day continuous 5-FU infusion and bolus mitomycin C. Proc Am Soc Clin Oncol 1982; 1:15

45. Ho DH, Frei E III: Clinical pharmacology of 1-β-D-arabinofuranosyl cytosine. Clin Pharmacol Ther 1971; 12:944-954

46. Goldie JH, Coldman AJ: A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979; 63:1727-1733

47. Goldie JH, Coldman AJ, Gudauskas GA: Rationale for the use of alternating non-cross-resistant chemotherapy. Cancer Treat Rep 1982; 66:439-449

48. Drewinko B, Green C, Loo TL: Combination chemotherapy in vitro with cis-dichlorodiammineplatinum(II). Cancer Treat Rep 1976; 60:1619-1625

49. Bergerat JP, Green C, Drewinko B: Combination chemotherapy in vitro—IV. Response of human colon carcinoma cells to combinations using cis-diamminedichloroplatinum. Cancer Biochem Biophys 1979; 3:173-180

50. Bergerat JP, Drewinko B, Corry P, et al: Synergistic lethal effect of cis-dichlorodiammineplatinum and 1-β-D-arabinofuranosylcytosine. Cancer Res 1981; 41:25-30

51. Markman M, Green MR, Pfeifle CE, et al: Combination intracavitary chemotherapy in patients with stage III-IV ovarian carcinoma failing standard treatment regimens. Proc Am Soc Clin Oncol 1983; 2:147

52. Markman M, Howell SB, Pfeifle CB, et al: Intraperitoneal chemotherapy with high dose cisplatin and cytarabine in patients with refractory ovarian carcinoma and other malignancies confined to the abdominal cavity. Proc Am Soc Clin Oncol 1984; 3:165

53. Markman M, Howell SB, Green MR: Combination intrapleural chemotherapy for malignant pleural disease. Proc Am Assoc Cancer Res 1984; 25:172